REMARKS

Claims 17-20 and 22-31 are currently active.

Claim 31 has been added.

Claim Rejections - 35 U.S.C. 102

Claims 17-20, 22-25, 29, and 30 were rejected under 35 U.S.C. 102(b) as being anticipated by Perlin et al.

Applicant is the author who actually wrote the Perlin et al. article, and personally performed or supervised all of the methods and results described therein. Applicant is therefore uniquely qualified to discuss the methods described in Perlin et al., as well as the features, utility and limitations of these methods.

Examiner states that:

(1) "Perlin et al. shows on pages 1200-1204 a mathematical method of analysis of a mixture of pooled DNA molecules from a plurality of individuals by generation through a polymerase chain reaction of a short terminal repeat loci."

(2) "Perlin et al. shows that it is possible to determine the genotype of a DNA molecule in the mixture by application of the method on pages 1207-1208."

(3) "The mathematical method comprises a matrix-vector analysis."

(4) "Perlin et al. shows methods of determining the optimum solution to obtain the correct genotype."

Applicant respectfully submits that examiner's second statement (2) is incorrect. Perlin et al. does not actually show any such method for determining the genotype of a DNA molecule in a mixture on pages 1207-1208. Rather, on those pages, Perlin et al. describes two distinct, inherently unrelated pooling methods.

The first method is "Pooled DNA Genotyping by Deconvolution". The key method steps from the two paragraphs in this section are:

(i) "Each pooled genotype comprised 100 alleles ... drawn from the marker's allele frequency distribution."
(ii) "... estimated the allele distribution vector x by using our pooled DNA deconvolution algorithms."
(iii) "The average mean squared errors between the estimated and known allele distribution vectors were then determined for our pooled DNA deconvolution algorithms (table 3)."
(iv) "... these allele-dependent deconvolution algorithms could prove acceptable candidates for determining allele frequencies in a population."

This first method, and its assessment and presentation in Perlin et al., is entirely focused on determining allele distributions from pooled DNA samples. There is no description

nor any indication in Perlin et al. of how this method could possibly be used in any way to determine the genotype of a single individual's DNA contained within a pooled DNA sample. The method produces an estimate of allele frequency for a pooled DNA population, but does not produce any type of individual genotype (allele or allele pair) for a single individual's DNA.

Moreover, the mathematical equations for this population method on page 1203 show (a) the loss of individual information by summation in large DNA pools, and (b) the application of stutter deconvolution to a single marker at a time, which works against using multiple markers to determine mixture weights and associated genotypes. Therefore, the first method is inherently incapable of determining the genotype of an individual from pooled DNA data.

The second method on page 1207 is "Pooled Marker Genotyping by Deconvolution". This method is designed to increase the number of markers that can be pooled in one gel readout lane. The pooling here refers to the markers, not to the DNA. The algorithm (page 1204, column 1, paragraphs 2-3) specifically refers to the "candidate diploid solution" for genotyping one individual at a time. The branch and bound algorithm described for pooled marker data is inherently inoperable when applied to mixed DNA samples. It is simply not possible to determine the genotype of an individual in a mixture by application of this second method.

The results presented for the second method on pages 1207-1208 report on experiments limited to determining the genotype of a simulated sample that contains only a

single individual. The construction of these simulated samples is described in section "Data Simulator" (pages 1204-1205). The results were assessed by comparing the five best branch-and-bound solutions to the known "correct genotype" of a single individual (page 1208, first paragraph). There is no mention anywhere in Perlin et al. of applying the second method for pooled markers to mixed DNA samples.

This detailed discussion of Perlin et al. demonstrates that it is not correct to say that:

> (ii) "Perlin et al. shows that it is possible to determine the genotype of a DNA molecule in the mixture by application of the method on pages 1207-1208."

Indeed, Perlin et al. provides no method whatsoever that could possibly determine the genotype of an individual in a mixture by application of the methods on pages 1207-1208. Therefore, since Perlin et al. does not describe any method for determining the genotype of an individual in a mixture, Claims 17-20, 22-25, 29, and 30 were not anticipated in any way by Perlin et al.

Applicant respectfully submits that these remarks fully address and adequately overcome examiner's rejections, and requests that Claims 17-20, 22-25, 29, and 30 now be allowed.

Claim Rejections - 35 U.S.C. 103

Claims 17-20, and 22-30 were rejected under 35 U.S.C. section 103(a) as being unpatentable over Perlin in view of Clayton et al.

Examiner observes that the claims are drawn to a method of determining the genotype of each DNA in a mixture of DNA molecules from a plurality of individuals suspected of perpetrating a crime. Examiner states that:

(1) "Perlin et al. shows on pages 1200-1204 a mathematical method of analysis of a mixture of pooled DNA molecules from a plurality of individuals by generation through a polymerase chain reaction of a short terminal repeat loci."

(2) "Perlin et al. shows that it is possible to determine the genotype of a DNA molecule in the mixture by application of the method on pages 1207-1208."

(3) "The mathematical method comprises a matrix-vector analysis."

(4) "Perlin et al. shows methods of determining the optimum solution to obtain the correct genotype."

However, Applicant has respectfully demonstrated in the preceding section that examiner's second statement (2) is incorrect. Perlin et al. does not actually show any such method for determining the genotype of a DNA molecule on pages 1207-1208. As examiner notes:

"Perlin et al. does not explicitly show results of genotyping from mixtures of DNA."

Indeed, Perlin et al. is entirely silent on methods of genotyping an individual from mixtures of DNA.

The Examiner combines Perlin et al. with Clayton et al. to suggest that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the method of Perlin et al. to analyze forensic samples. Examiner reasoning includes the assertion:

"Perlin et al. shows that their method can be used to determine genotypes of individuals from whom mixed DNA samples were derived."

However, this assertion is not correct. As established in the preceding section, Perlin et al. does not actually show any such method for determining the genotype of an individual from whom mixed DNA samples were derived. Indeed, the methods described in Perlin et al. are entirely inoperable in performing such a genotype determination of an individual in a DNA mixture.

The Examiner suggests that "Clayton et al. shows general methods and working examples of determining genotypes of individuals from mixed DNA samples." It is not entirely

evident that Clayton et al. actually show such a general method. Regardless, the methods of Clayton et al. do not:

"derive a mathematical solution by performing a matrix operation on linear equations" (claim 17, step c),

and so do not in any way anticipate the claimed invention.

Perlin et al. provides no enablement for "determining the genotype at a locus of an individual contained in the DNA mixture" (claim 17, step d). So Perlin et al. has no feasible combination with Clayton et al.'s analysis of forensic samples. Therefore, it would not have been at all obvious to one skilled in the art at the time the invention was made to use the method of Perlin et al. (which is inherently inoperable as a method in isolation for genotyping individuals in a DNA mixture) for analyzing the mixed forensic DNA samples described by Clayton et al. Since the combination could not work, there would have been no obvious motivation (nor any feasible mechanism) to combine Perlin et al. and Clayton et al. in the way that Examiner suggests.

Applicant respectfully submits that these remarks fully address and adequately overcome examiner's rejections, and requests that Claims 17-20, and 22-30 now be allowed.

Response to Arguments

Examiner states that "Perlin et al. shows deconvolution of pooled marker DNA on page 1203". It is the *markers* that are pooled in this method of Perlin et al., not the individual DNA samples. Therefore, the cited method is not relevant to analyzing DNA mixtures, nor is it relevant to the claimed invention, whose steps specifically relate to DNA mixtures, e.g. (Claim 17):

(a) obtaining DNA profile data of a sample that comprises a DNA mixture of two or more individuals;

(b) representing the data and a genotype of the individuals contained in the DNA mixture in a set of linear equations;

(d) determining the genotype at a locus of an individual contained in the DNA mixture from the mathematical solution.

The Examiner states that Perlin et al. "shows a working example of deconvolution of genotypes on pages 1207-1208".

In the first method on page 1207 (Pooled DNA Genotyping by Deconvolution), the deconvolution of the pooled DNA data produces an "allele distribution," not a genotype of an individual. The allele distribution used here corresponds to the distributions of 100 alleles at a locus. However, the genotype of an individual corresponds to 2 alleles at a locus. Clearly, these are two entirely distinct problems whose described methods are not interoperable.

In the second method on page 1207 (Pooled Marker Genotyping by Deconvolution), the deconvolution of the pooled marker data is performed on DNA data from a *single* individual, not on a DNA mixture formed from a plurality of individuals. The marker pooling is done to increase the number of simultaneous experiments that can be performed in one sequencer lane on one individual -- it has nothing to do with DNA mixtures or pooled DNA samples. The pooled marker deconvolution algorithm is so combinatorially complex (see page 1208, second paragraph) that it would be entirely inoperable on a mixed DNA sample.

The Examiner states that "in the discussion on pages 1208-1209, Perlin et al. states that the method can be used for deconvolution for both single genotype applications and pooled genotyping".

In fact, the discussion (page 1208, column 2, paragraph 2) states that the three different methods described in Perlin et al. "were applied in three different situations," as follows:

(1) *Single-genotype* analysis. This entails no pooling of DNA samples, and therefore does not refer in any way to Claim 17 (d) "determining the genotype at a locus of an individual contained in a DNA mixture".

(2) *Pooled DNA* genotype analysis. This method entails "determining allele frequency distributions." Determining the frequencies of large numbers of alleles is entirely unrelated to determining the genotype of an individual who has only two alleles. Hence it does not refer in

any way to Claim 17 (d) "determining the genotype at a locus of an individual contained in a DNA mixture".

(3) *Pooling markers* having overlapping size windows. This method entails inferring genotypes from "pooled marker data" -- the markers are pooled, not the DNA samples. Since there is no pooling of samples into a DNA mixture, the method does not refer in any way to Claim 17 (d) "determining the genotype at a locus of an individual contained in a DNA mixture".

The Examiner states that "Clayton et al. further show determination of genotypes of individuals from mixed DNA samples". Clayton et al. present no clear algorithm for accomplishing this result. Clayton et al. do not use linear equations, matrix operations or mathematical solutions. Therefore, Clayton et al. is not relevant to the claimed invention, whose steps specifically relate to such a mathematical approach, e.g. (Claim 17):

(b) representing the data and a genotype of the individuals contained in the DNA mixture in a set of linear equations;

(c) deriving a mathematical solution by performing a matrix operation on the linear equations; and

(d) determining the genotype at a locus of an individual contained in the DNA mixture from the mathematical solution.

Double Patenting and Terminal Disclaimer

Examiner provisionally rejected claims 17-20 and 22-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5-8, and 21 of co-pending Application No. 09/776,096 in view of Perlin et al.

Applicant had disclaimed an improperly identified application using an incorrect number to identify the application being disclaimed.

A terminal disclaimer has been filed herewith using the correct identification number 09/776,096 in compliance with 37 CFR 1.321(c) to overcome the provisional rejection, since the conflicting application is commonly owned with this application.

In view of the foregoing amendments and remarks, it is respectfully requested that the outstanding rejections and objections to this application be reconsidered and withdrawn, and Claims 17-20 and 22-31, now in this application be allowed.

CERTIFICATE OF MAILING

I hereby certify that the correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on 3/9/04

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